REMARKS

Claims 3-6 are pending in the Application. In the Office Communication mailed on December 21, 2010, the Examiner made two rejections:.

I. Claims 4 and 6 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; and

II. Claims 3 and 5 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Floudas et al. (US Patent No 6,832,162) in view of Maier et al. (Eur Biophys K Biophys LETT (1999), see citation #27 of IDS filed 04/28/2010).

35 U.S.C. §112, second paragraph

I. Claims 4 and 6 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner asserts that Claims 4 and 6, which are directed to methods, are confusing with respect to reciting use of the processors of Claims 3 and 5, respectively. For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claim 4 is herein amended to delete reference to Claim 3 and to recite the process steps performed in a method. Similarly, Claim 6 is herein amended to delete reference to Claim 5 and to recite the process steps performed in a method.

Applicants respectfully submit that the claims as amended satisfy the requirements of 35 U.S.C. 112, second paragraph and request that this rejection be withdrawn.

35 U.S.C. §103

II. Claims 3 and 5 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Floudas et al. (US Patent No 6,832,162) in view of Maier et al. (Eur Biophys K Biophys LETT (1999), see citation #27 of IDS filed 04/28/2010). Applicants respectfully disagree. The Floudas patent relates to a system for predicting protein structures, not nucleic acid structures. The Examiner seems to be relying on it only for the global concept of analyzing a primary sequence for motifs (alpha helices, beta sheets, coils), as a step in solving a larger tertiary structure problem, though not a structure problem related to nucleic acid analysis.

Applicants note that the secondary structure elements in nucleic acid are double stranded and hence are very different from the single stranded motif elements found in proteins (namely alpha helices and beta strands). As a result of this difference, methods for selecting nucleic acid motifs for structure building, for connecting motifs together into larger structures, and for storing motif information are very different than the methods used for protein structure analysis and storage. Further, the nature and variety of motifs in nucleic acid structures are very different, and comprise motifs of different lengths and of different conformations, including, *e.g.*, base pairs, hairpin loops, internal loops, bulges and multi-branched loops and bifurcations.

Maier describes the use of a force field based method for is analyzing very short oligonucleotides each comprising a single four basepair stem and a single tetraloop (4 nucleotides). As specifically noted by Maier, the MC-SYM method used to generate the structures is extremely CPU intensive - so much so that they did conformational searches only on the 4 nt loops, not on the entire 12-mer oligonucleotides (Maier, p566, col 2). The tetramer conformations were then fit to stem structures that were assumed, not modeled, prior to application of the JUMNA energy minimization algorithm (id). As discussed in the specification of the instant application, the computational intensity MC-SYM limits its utility for modeling large RNA structures (Specification, page 3, lines 7-13).

While Maier makes reference to the concept of a "tool kit" of RNA structural motifs (Maier, p565 col 1), Maier teaches the analysis of only a single form of structure motif and does not teach or suggest how one would build a more complex tertiary RNA structural model from multiple motifs, even taking the general teachings of Floudas into consideration. Neither Floudas nor Maier provide guidance on how to assemble candidate tertiary structures from a plurality of motif structures, how to refine predicted tertiary structures, or how to select a refined candidate three-dimensional structure based on best calculated energy to predict a three-dimensional structure of said test nucleic acid, as recited in Claims 3 and 4.

For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claims 3 and 4 are amended herein to recite that the energy minimization algorithm conducted by the processor of Claim 3, and used in the method of Claim 4 comprises:

i. calculating energy minimization terms for said three-dimensional composite structure, said energy minimization terms comprising bond stretching, bond angles,

torsion stress, and non-bonded interactions;

ii. optimizing force constants, distance dependence, partial charges, and van der Waals radii parameters;

iii. accounting for gap penalties for insertions or deletions, if present in said candidate three-dimensional composite structure;

iv. accounting for one or more experimental constraints associated with said test nucleic acid, said experimental constraints comprising hydrogen bonding information, position of phosphorus atoms, nuclear Overhauser effect information, residual dipolar coupling information, x-ray crystallographic electron density, cryo-electron microscopy information, and chemical probing information;

v. employing distance constraints within a defined distance range but ignoring distance constraints outside of said defined distance range;

vi. accounting for one or more nucleic acid folding thermodynamic measures, said nucleic acid folding thermodynamic measures comprising: folding entropy, solvation entropy changes, enthalpy changes, and free energy changes, and

vii. accounting for known interactions, said known interactions comprising interactions with: proteins, metal ions, or other ligands by setting anchor points;

Neither Floudas nor Maier teach or suggest use of an energy minimization algorithm comprising the recited features. The JUMNA algorithm taught by Maier reduces the complexity of the analysis by specifically excluding use of a bond stretching term, and instead uses bond lengths fixed at optimum values (Maier 566, col 2; 577, col 1). This contrasts with the instant claims, which recite that the energy minimization terms comprise a bond stretching term.

Regarding Claims 5 and 6, the Examiner states only that Claim 5 is directed to a system comprising a configured processor for generating a nucleic acid structural motif database comprising only the steps of receiving nucleic acid physical structure information, decomposing said information into nucleic acid structural motifs, associating the data with said structure motifs, comparing structures to existing motifs in said database, and adding sad structure to said database. The Examiner does not point to a processor configured to execute the steps recited in Claim 5, or a method making use of the process steps.

For business reasons and without acquiescing to the Examiner's arguments, and reserving

the right to prosecute the original or similar claims in one or more future applications, Claim 5 is amended herein to recite systems and methods related to three-dimensional nucleic acid structure motifs, and for clarity to recite a system for populating a nucleic acid three-dimensional structure motif database. Neither Floudas nor Maier teach or suggest the system comprising a processor configured to execute the process for populating a database of nucleic acid three-dimensional structure motifs, as recited in Claim 5, or a method making use of such a processor, as recited in Claim 6.

Nonobviousness is decided as a matter of law based on four factual inquiries as explained in *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and reaffirmed in *KSR International, Inc. v. Teleflex, Inc.*, 550 U.S. 398 (2007). The patent examiner is responsible for evaluating the claimed invention against the most relevant prior art from the viewpoint of a person of ordinary skill in the field of invention. See *Graham*; *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009); see generally *In re Oetiker*, 977 F.2d 1443, 1445–47 (Fed. Cir. 1992). While KSR relaxed some of the formalism accompanying earlier decisions requiring a "teaching, suggestion, or motivation" to combine prior art references, even under the "expansive and flexible approach" established by *KSR* (550 U.S. at 401, 415), a valid prima facie case of obviousness still requires the Office to cite a reference, or a combination of references, that discloses or suggests each and every element of the claimed invention. See *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995); *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003); *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974).

While not acquiescing that the other requirements for establishing prima facie obviousness have been met, for the reasons recited above Applicants submit that the combination of cited references fails to establish prima facie obviousness of Claims 3-6 because the cited art fails to teach each of the elements of the instant claims. Applicants therefore respectfully request that this rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Dated: June 21, 2011

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